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TSAY, MARSHA M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,878	VAN ES ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9-28 and 30-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9-28 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

This Office action is in response to Applicants' remarks received May 22, 2009.

Applicants' arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 2, 8, 29 are canceled. Claims 1, 3-7, 9-28, 30-32 are currently under examination.

Priority: The request for priority to EPO 03077451.7, filed August 5, 2003, is acknowledged.

Objections and Rejections

Claims 22, 27 are objected to because of the following informalities: claim 22 is dependent on a canceled claim (i.e. claim 2); claim 27 recites the glass transition temperature can be selected from the group consisting of about 5 degrees Celsius, about 10 degrees Celsius. Claim 27 is dependent on claim 24, which already recites the glass transition temperature is at least 10 degrees Celsius. Appropriate correction is required.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-7, 9-28, and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al. (WO 0134801; IDS, previously cited) in view of Wang (Wang 2000 International Journal of Pharmaceutics 203: 1-60; previously cited) as evidenced by Cortesi et al. (1998 Biomaterials 19: 1641-1649). Cortesi et al. has been used as evidence that mammalian gelatins have a glass transition temperature of 180-200° C (p. 1647).

Chang et al. disclose vaccines comprising recombinant gelatin and a method of producing such vaccines. Chang et al. disclose a dried vaccine formulation comprising recombinant gelatin (p. 85 line 9, p. 86 line 29; claim 1) or lyophilized vaccines comprising using recombinant gelatin as a stabilizer (p. 61 lines 35-38; claim 1). Accordingly, the recombinant gelatin is essentially a polymer that stabilizes the pharmaceutical formulation and should have characteristics similar to an animal-source gelatin, i.e., MW, melting temperature, thermal stability etc. (p. 65 lines 5-6, 21-33). Therefore, the use of recombinant gelatin offers the advantage of reducing the risk of unwanted immune responses from the gelatin itself (p. 59 lines 12-19). Chang et al. disclose the recombinant gelatin can be derived from a human sequence or animal sources (p. 59 lines 16-19), wherein the term "derivative" encompasses those molecules containing at least one structural and/or functional characteristic of the molecule from which it is derived (p. 15 lines 11-15). It is known that gelatin comprises consecutive Gly-Xaa-Yaa triplets. The recombinant gelatin can have a molecular weight range between 0 kDa to 350 kDa, for example 0 to 60 kDa (p. 64 liness 19-21, 85 lines 22-26; claim 3). Chang et al. also disclose a method of producing a composition comprising a vaccine and recombinant gelatin (p. 88 lines 25-32; claim 9). In a non-limiting example, i.e. Example 4, Chang et al. disclose the expression of a non-hydroxylated recombinant human gelatin, which would therefore be free of a helical

structure (p. 73 lines 5-10; claims 1, 6-7, 15-20). Further, Chang et al. disclose the recombinant gelatins can possess particular ranges of molecular weights (p. 63 lines 30-32, example 1; claims 5, 12-14). Chang et al. do not teach a glass transition temperature for gelatin.

Wang et al. disclose that lyophilized proteins need stabilization in the solid state to survive long-term storage as pharmaceuticals (p. 25 col. 2). Accordingly, the glass transition temperature of protein formulations is considered to be one of the major determinants of protein stability (p. 28 col. 2). Wang et al. disclose that generally the higher the glass transition temperature of the polymer in said formulation, the more stable the protein formulation; therefore, the glass transition temperature may be used as a guiding parameter to screen protein stabilizers, i.e. by DSC (differential scanning calorimetry) (p. 28 col. 2 to p. 29 col. 1). In Tables 1 (p. 19) and 2 (p. 39), Wang et al. disclose gelatin can be used as a polymer to stabilize lyophilized pharmaceuticals.

It is known in the art that mammalian gelatins have a glass transition temperature of 180-200° C (evidenced by Cortesi et al., p. 1647)

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Chang et al. by producing a lyophilized composition comprising a protein drug and a recombinant gelatin such that said recombinant gelatin has a polypeptide sequence that is identical to a region of a native human collagen sequence having a high glass transition temperature (as suggested by Wang), where said recombinant gelatin has the same functional and/or structural characteristics as said native gelatin, i.e. having a glass transition temperature of 200° C (as evidenced by Cortesi et al.) (claims 1, 3-7, 9-28, 30-32). Since Chang et al. disclose that recombinant gelatin comprising a native collagen sequence can

minimize immune response and can be used as a stabilizer for improving thermal stability in lyophilized vaccine formulations, and Wang further discloses that polymers having a high glass transition temperature provide the most stability to a protein formulation, one of ordinary skill would be motivated to produce a recombinant gelatin that has a high glass transition temperature at least equivalent to native gelatin (i.e. 200° C) or higher than 200° C since Wang discloses that generally the higher the glass transition temperature of a polymer determined by DSC, the more stability it imparts on a lyophilized pharmaceutical composition.

Regarding the limitations of claims 24 and 31, i.e. selecting a region of the amino acid sequence of a native collagen having a calculated average glass transition temperature higher than the calculated average glass transition temperature of the complete native collagen by at least 10 degrees Celsius, it should be noted that since gelatin is hydrolyzed collagen, its amino acid sequence would only contain a region of the complete amino acid sequence of native collagen and in view of Wang, it would be reasonable for one of ordinary skill to select a gelatin having a glass transition temperature at least equivalent to native gelatin (i.e. 200 ° C) or higher than 200° C, which would mean the glass transition temperature is at least 10 degrees Celsius greater than the complete native collagen.

The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969). In this instance, the motivation would be to produce a recombinant gelatin sequence having a mammalian gelatin sequence that also has a glass transition temperature at least

equivalent to native gelatin such that said recombinant gelatin can be used to make the most stable lyophilized protein formulation.

In their remarks, Applicants assert (1) claims 1 and 9 are now limited to using a recombinant or synthetic gelatin-like polypeptide stabilizer that has a molecular weight between 3,000 Da and 80,000 Da. Therefore, having regard to the new molecular weight limitation appearing in claims 1 and 9, grounds of rejection based upon disclosures of such full-length native collagen sequences are now moot, Applicants submit. (2) The glass transition temperature (Tg) for a food gelatin described by Matveev et al. do not appear to be that of a hydrolyzed gelatin compound that might have been used as a protein stabilizer. Rather, the Tg provided by Matveev et al. appear to be that of a native non-hydrolyzed food gelatin. However, such a full-length recombinant gelatin is now excluded from the scope of claims 1 and 9 by the limitation of the molecular weight to be between 3,000 and 80,000 Da, and the Tg of hydrolyzed gelatin, which was known as a stabilizer in pharmaceutical compositions, was unknown to a skilled person, prior to Applicants' claimed invention, Applicant believes. (3) Chang et al. do not provide knowledge of the relationship between the glass transition temperature and the improved stability of a lyophilized physiological composition that can be obtained by employing in the lyophilized composition a recombinant or synthetic polypeptide. Chang et al. do not disclose a synthetic or recombinant gelatin-like polypeptide having a glass transition temperature higher than 180° C or a method of preparing such a polypeptide. (4) Wang does not correct the deficiencies of Chang et al. Wang et al. identifies glass transition temperature as one of a number of factors that can affect the stability of solid protein pharmaceuticals (Wang et al. p.

28). Accordingly, Wang does not provide clear guidance or suggestion to a person of ordinary skill in the art that the stability of a lyophilized pharmaceutical composition can be improved by employing a synthetic or recombinant-like polypeptide having a calculated glass transition temperature higher than 180° C. Rather, the number of stability-related factors identified by Wang and the nature of the discussion would suggest to a person of ordinary skill that controlling the stability of a solid protein pharmaceutical is a complex problem. (5) Wang mentions gelatin in Table 1 on page 19; however, no Tg is given for the gelatin of Wang. (6) Wang's guidance regarding the role of glass transition temperature in the stability of solid protein pharmaceuticals is equivocal. Applicants cite p. 29 of Wang, where mixed results have been obtained and some formulations with a lower Tg are more stable, according to Wang.

Applicant's arguments have been fully considered but they are not persuasive.

(1) Reply: Firstly, the distinction between gelatin and collagen needs to be noted. It is well known in the art that gelatin is hydrolyzed collagen. Therefore, gelatin would have a molecular weight that is distinctly lower than the 140,000 Da of instant SEQ ID NO: 1 (human Col1A1) (Applicants' remarks 05.22.09, p. 13). Chang et al. disclose recombinant gelatin is used as a stabilizer in lyophilized vaccine compositions, i.e. a lyophilized composition comprising an active pharmaceutical. Chang et al. disclose the recombinant gelatins used can range from MW of 0 to 60 kDa (p. 64 lines 19-21). Therefore, the gelatin of Chang et al. would meet the instant molecular weight of 3,000 Da to 80,000 Da (claim 1) since "where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a prima facie case of obviousness exists" (MPEP 2144.05) as well as the instant limitation that the gelatin polypeptide is identical to or essentially similar to a selected region of the amino acid sequence of a native collagen (claim 24).

(2) Reply: Necessitated by applicant's amendment, the Matveev et al. reference has been withdrawn and replaced with the Cortesi et al. reference which discloses that mammalian gelatins have a calculated glass transition temperature of 180-200° C. Since gelatin is hydrolyzed collagen, it would have a molecular weight below collagen. It is not clear what Applicants' mean by "hydrolyzed" gelatin and "non-hydrolyzed" gelatin (in their remarks of 05.22.09) since gelatin is hydrolyzed collagen.

(3) Reply: Chang et al. disclose that the recombinant gelatins can be used as a stabilizing agent for vaccines, including improving their thermal stability even when said vaccines are subjected to high temperatures for long periods (Chang et al. p. 65 lines 5-6). Wang et al. disclose that lyophilized proteins need stabilization in the solid state to survive long-term storage as pharmaceuticals (p. 25 col. 2). Further, Wang et al. disclose that generally the higher the glass transition temperature of the polymer in said formulation, the more stable the protein formulation; therefore, the glass transition temperature may be used as a guiding parameter to screen protein stabilizers, i.e. by DSC (differential scanning calorimetry) (p. 28 col. 2 to p. 29 col. 1). Therefore, the deficiency of Chang et al. to disclose a glass transition temperature of gelatin is remedied by Wang.

(4) Reply: Wang discloses DSC is the most widely used method for determining Tg of a polymer (Wang p. 28). Wang further disclose that polymers, including gelatin, have been used to stabilize proteins during the lyophilization process (p. 11). Therefore, it would appear that Wang provides adequate guidance to determine the Tg of a polymer, i.e. gelatin, that is to be used in a pharmaceutical composition. Therefore, since Chang et al. disclose recombinant gelatin from various mammalian sources can be used to stabilize a lyophilized pharmaceutical

composition, and it is known in the art that gelatin is hydrolyzed collagen and would naturally consist essentially of a region of native mammalian collagen, it would have been obvious to one of ordinary skill to determine the Tg of gelatins by DSC in order to use gelatins with the highest Tg since Wang discloses that generally, the higher the Tg, the more stable the protein formulation will be.

(5) Reply: The deficiency of Wang to disclose a Tg for gelatin is remedied by the evidence of Cortesi et al., which disclose mammalian gelatins have a glass transition temperature of 180-200° C.

(6) Reply: Firstly, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed.." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). See also MPEP § 2123.

The portions of Wang cited by Applicants, *i.e.*, some formulations with a lower Tg are more stable (p. 29), are referring to sugar formulations. It should be noted that gelatin is a protein polymer and not a sugar polymer. Nevertheless, on page 36, first column second paragraph, Wang discloses polymers may stabilize proteins by increasing Tg of a solid protein formulation, because polymers usually have higher Tgs due to their molecular weights. Therefore, Wang is not equivocal regarding the role of glass transition temperature in the stability of solid protein pharmaceuticals. Wang clearly notes that protein polymers, including gelatin, can be used as stabilizers in lyophilized protein formulations, wherein a protein polymer with a higher glass transition temperature will result in a more stable protein formulation.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claims 4-7 be found allowable, claims 10, 12, 15, 19 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is (571)272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

August 14, 2009

/David J. Steadman/
Primary Examiner, Art Unit 1656